The Skinny on Pharmacologic Management of Obesity

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Weight Curve

48 yo woman
BMI: 44 kg/m²
OSA, OA knee

24 hour urine Cortisol, TSH—NL

Body Weight (lbs)


150 200 239 241 261 287
Weight Management: Chronic Disease Model

- Update on Physiology and Pathophysiology of Weight Regulation
- Treatment of Overweight and Obesity
  - Lifestyle (diet and exercise)
  - Medications
  - Bariatric Surgery

Body Weight Set Point is Receives Signals from Gut Hormones During Meal

- ↑ Ghrelin
- ↓ Hunger
- ↑ PYY
- ↑ insulin/amylin
- ↑ GLP-1
- ↑ CCK

CNS Body Weight Regulation Center Receives Adiposity and Meal-related Signals

“Are you weighing what I think you should?”

“Are you eating enough (or too much) to maintain that weight?”

Weight Management: Chronic Disease Model

Weight Management Specific Practice Tips:
- Use “people-first” language: Patients “with obesity” vs. “are obese.”
- Create a “weight history” to identify:
  - Onset of unwanted weight gain
  - Sudden jumps
  - Timing to specific meds, medical diseases
  - Relationship to pregnancy, menopause
  - Lifetime max
  - Any previous strategies that had been successful
  - Current weight
- Identify and code for any obesity-related complication that is covered
Obesity is associated with >230 complications

Obesity is associated with multiple complications
Metabolic, Mechanical and Mental

METABOLIC
- Type 2 diabetes
- Prediabetes
- Gestational diabetes
- Dyslipidaemia
- High blood pressure
- Coronary artery disease
- Atrial fibrillation
- Heart failure

MECHANICAL
- Stroke
- Sleep apnoea
- Heart failure
- Fatty liver
- Gallstones
- Infertility
- Incontinence
- Joint disease

MENTAL
- Depression
- Anxiety
- Asthma
- Infertility
- Depression
- Anxiety
- Gout
- 2 diabetes
- Prediabetes
- Chronic back pain

CANCERS*
- Gout
- Asthma
- Gallstones
- Infertility
- Incontinence
- Joint disease
- Heart failure
- Fatty liver
- Sleep apnoea

PHYSICAL FUNCTIONING
- Depression
- Anxiety
- Asthma
- Infertility
- Depression
- Anxiety
- Gout
- 2 diabetes
- Prediabetes
- Chronic back pain

*Including breast, colorectal, endometrial, esophageal, kidney, ovarian, pancreatic and prostate
Weight Management: Chronic Disease Model

- Update on Physiology and Pathophysiology of Weight Regulation
- Treatment of Overweight and Obesity
  - Lifestyle (diet and exercise)
  - Medications
  - Bariatric Surgery

Question

Which of the following diet and/or diet + exercise approaches is best for weight loss and health?

1. Low-carbohydrate diet?
2. Low-fat diet?
3. Keto diet?
4. High-protein diet?
5. Diabetes Prevention Program?
Weight Loss
Comparison of “Named Diets.”

Average weight loss: 2–3%

Diabetes Prevention Program: Modest Effect on Weight (Low-fat Diet + Exercise)

Four year weight loss: 4%
Diabetes Incidence Best Lowered by Lifestyle (Low-fat Diet + Exercise)

Question

Which of the following diet and/or diet + exercise approaches is best for weight loss and health?

1. Low-carbohydrate diet?
2. Low-fat diet?
3. Keto diet?
4. High-protein diet?
5. Diabetes Prevention Program?
Lifestyle Recommendations

Eat food. Mostly plants. Not too much.

Be active. At work. At home.

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Weight Management: Chronic Disease Model

- Update on Physiology and of Pathophysiology of Weight Regulation
- Treatment of Overweight and Obesity
  - Lifestyle (diet and exercise)
  - Medications
  - Bariatric Surgery
Recommendation For Consideration of Pharmacological Weight Management

- BMI 27 - 30 kg/m² and a weight-related comorbidity:
  - HTN
  - Dyslipidemia
  - Diabetes
  - Other

OR

- BMI ≥ 30 kg/m²


Pharmacological Weight Management

The Science of Obesity Management: An Endocrine Society Scientific Statement

(Endocrine Reviews. 39: 79 – 132, 2018)
Pharmacological Weight Management

Currently FDA Approved Medications for Weight Loss

- **tetrahydrolipstatin** (Orlistat) $$$
  - (now over the counter as “alli”-60 mg dose)

- **phentermine** (Fastin, Ionamin, Adipex) $
- **phentermine + topiramate** (Qsymia) $ or $$$
- **lorcaserin** (Belviq) $$$
- **bupropion + naltrexone** (Contrave) $
- **liraglutide 3.0** (Saxenda)

Pharmacological Weight Management: Tips

- **Lifestyle** is always attempted first and continued during treatment.
- All drugs are **Category X** for Pregnancy and Lactation.
- All drugs have been shown to **improve cardiometabolic risk factors**.
- Weight loss is **variable**.
- Continue treatment long-term (do not stop) unless:
  - Patient is a non-responder
  - Side effect(s) emerge
- **Avoid** use of phentermine, phentermine/topiramate ER, and bupropion/naltrexone SR in patients with:
  - Active CAD/CHF
  - Untreated HTN
  - Untreated hyperthyroidism
  - MAO inhibitors
- **Hypoglycemia** is a risk in patients with diabetes treated with oral hypoglycemic med and insulin
Weight Loss Medications Enhance CNS Signaling to Meal-related Signals

- phentermine
- phentermine + topiramate
- lorcasarin
- bupropion + naltrexone
- liraglutide

↓ CNS Hunger Signaling

↑ CNS Satiety Signaling

Weight Loss Medications with Phentermine

- 8 mg tablets 2-3 times daily (Lomair)
- 37.5 mg tablets daily (Adipex-P)
- 15 and 30 mg capsules daily

-9-10%
Phentermine: Side Effects and Precautions

Short-Term: Central Adrenergic Agonism
- Insomnia
- Dry mouth
- Increased heart rate and BP
- Anxiety

Long-term:
- BP stable or reduced with weight loss
- Addictive behaviors not demonstrated
- Can be continued more than 6-12 weeks

per Qsymia package insert: “...an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients...”

American Journal of Therapeutics (2011) 18, 292–299

Weight Loss with Phentermine + Topiramate (Qsymia)
Cardiovascular Safety During and After Use of Phentermine and Topiramate

Table 3. Adjusted IRRs and IRDs for MACE and Components of This Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>PHEN/TPM</th>
<th>Fixed-PHEN/TPM</th>
<th>PHEN</th>
<th>TPM</th>
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<tbody>
<tr>
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<td>Current Use</td>
<td>Unexposed (Reference)</td>
<td>Current Use</td>
<td>Unexposed (Reference)</td>
</tr>
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<td>Person-years</td>
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<td>232,470</td>
<td>2207</td>
<td>217,065</td>
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<td>395</td>
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<td>IRR (95% CI)</td>
<td>0.57 (0.19 to 1.78)</td>
<td>0.24 (0.03 to 1.70)</td>
<td>0.56 (0.34 to 0.91)</td>
<td>1.58 (1.33 to 1.87)</td>
</tr>
<tr>
<td>IRD (95% CI)</td>
<td>-1.83 (-2.03 to -1.44)</td>
<td>-1.43 (-1.87 to -0.30)</td>
<td>-0.02 (1.02 to -0.22)</td>
<td>1.11 (0.64 to 1.57)</td>
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<tr>
<td>IRR (95% CI)</td>
<td>0.35 (0.05 to 2.52)</td>
<td>0.00 (0.00 to NC)</td>
<td>0.51 (0.26 to 1.00)</td>
<td>0.79 (0.59 to 1.07)</td>
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<tr>
<td>IRD (95% CI)</td>
<td>-0.66 (-1.37 to 0.06)</td>
<td>-1.02 (-1.20 to -0.85)</td>
<td>-0.39 (-0.68 to -0.10)</td>
<td>-0.22 (-0.48 to 0.04)</td>
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<tr>
<td>IRD (95% CI)</td>
<td>-0.16 (-1.10 to 0.92)</td>
<td>-0.37 (-1.29 to 0.54)</td>
<td>-0.23 (-0.49 to 0.03)</td>
<td>1.38 (1.01 to 1.76)</td>
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<td>CV-related death</td>
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<td>0.00 (0.00 to NC)</td>
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<td>IRD (95% CI)</td>
<td>-0.04 (-0.07 to -0.02)</td>
<td>-0.04 (-0.06 to -0.02)</td>
<td>0.00 (-0.09 to 0.09)</td>
<td>-0.06 (-0.12 to 0.00)</td>
</tr>
</tbody>
</table>

MACE variables: hospitalization for AMI or stroke and in-hospital CV-related death

25

Weight Loss With Lorcaserin (5-HT<sub>2C</sub> agonist)

A. Weight Loss

Change in weight from baseline (kg) vs. Months since Randomization

Placebo

Lorcaserin

~4 %
Non-inferiority of Lorcaserin (5-HT$_{2C}$ agonist) on MACE

Weight Loss With Bupropion + Naltrexon (Contrave)
Effect of Bupropion + Naltrexon (Contrave) on MACE

Liraglutide 3.0 for Weight Management and Type 2 Diabetes Risk Reduction in Pre-diabetes
Liraglutide 3.0 for Weight Management and Type 2 Diabetes Risk Reduction in Pre-diabetes

LEADER: Liraglutide 1.8 mg Improves Cardiovascular Outcomes and All Cause Mortality in Type 2 Diabetes
48 yo woman
BMI: 44 kg/m²
OSA, OA knee
TC: 204
TG: 319
LDL: 147
HDL: 25
A1c: 6.4%

Phentermine:
18.75 → 37.5 mg
**Weight Curve: Next Steps**

- **Body Weight (lbs)**
  - 2005: 150
  - 2006: 200
  - 2013: 239
  - 2015: 241
  - 2016: 261
  - May-17: 287
  - Oct-17: 266
  - Apr-18: 245

- **Phentermine**
  - 18.75 → 37.5 mg

- **Topiramate**
  - 25 → 100 mg BID

- **24 hour urine Cortisol—NL**

- **Biochemistry**
  - **TC:** 204
  - **TG:** 319
  - **LDL:** 147
  - **HDL:** 25
  - **A1c:** 6.4%

- **TC:** 196
  - **TG:** 134
  - **LDL:** 135
  - **HDL:** 34
  - **A1c:** 5.5%

- **BP:** 107/55
Question

What do you recommend next regarding weight loss medications?

1. Continue phentermine for 3 months then stop?
2. Continue both for 1 year then stop and monitor?
3. Continue indefinitely?
4. Begin intermittent therapy (every other month)?
Weight Curve: Example of Using Rx for Weight Stability

Body Weight (lbs)

Year Follow-up

0 3 10 11 12

MediFast
Daily exercise

Phentermine:
18.75 → 37.5 mg
Weight Curve: Example of Using Rx for Weight Stability

Pharmacological Weight Management: The Skinny

- **Obtain a lifetime weight history**
- **Lifestyle** is always attempted first and continued during treatment.
- Once weight Rx started, weight loss is **variable and modest (4-10%)**. 
  
  *Think management of hypercholesterolemia before statins and hypertension before ACEI*
- Continue treatment long-term (do not stop) unless:
  - Patient is a non-responder (a "responder" may maintain weight)
  - Side effect(s) emerge
- **Refer to bariatric surgery** when appropriate
  - BMI $\geq 35$ kg/m$^2$ + comorbidity
  - BMI $\geq 40$ kg/m$^2$
### Reasons for Underutilization of Weight Management Medications

- Previous weight loss drugs had poor safety record (fenfluramine, sibutramine, rimonabant)
- Perceived need for frequent follow-ups needed for AE monitoring
- Some are controlled substances:
  - Phentermine and lorcacerin are DEA schedule IV (low potential for abuse and low risk of dependence)
- Need for long term use
  - Goal ≥ 3% weight loss at 3 months; ≥ 5% at 1 year
- Variable response among patients, including many "non-responders"
- Poor and inconsistent insurance coverage
  - Often cost to patient

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**Thank You**